Individual Safety Report

3723700-5-00-01

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

for use by user-facilities, distributors and manufacturers for MANDATORY reporting
Novartis Pharmaceuticals

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Relsys International, Inc
FDA Facsimile Approval 30-JUN-1999

MFR report # PHBS1999US10870

UF/Dist report #

FDA Use Only

A. Patient information

1. Patient identifier	2. Age at time of event / or Date of birth	3. Sex	4. Weight
UNK in confidence	19 Years or UNK	[X] female [ ] male	58.9 lbs or 26.7 kgs

B. Adverse event or product problem

1 [X] Adverse event and/or [ ] Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)

[X] death UNK (mo/day/yr)
[ ] life-threatening
[ ] hospitalization - initial or prolonged
[ ] disability
[ ] congenital anomaly
[ ] required intervention to prevent permanent impairment/damage
[ ] other:

3. Date of event	4. Date of this report
UNK	05/08/2001

5. Describe event or problem

HEPATIC FAILURE[Hepatic failure]
INTOXICATION[Therapeutic agent toxicity]

Case Description:
This case was previously recorded as 99HQ-10473 ;
THIS IS A LITERATURE REPORT:
THE PATIENT TOOK CARBAMAZEPINE, ACETAMINOPHEN AND VALPROIC ACID AND DEVELOPED AN ACETAMINOPHEN INTOXICATION AND HEPATIC FAILURE. THE PATIENT DIED. A FULL ENGLISH LITERATURE TRANSLATION IS AWAITED.

FOLLOW-UP INFORMATION WAS RECEIVED ON 01 DEC 1999 IN FORM OF A LITERATURE TRANSLATION:
THE PATIENT WAS IN A NURSING FACILITY BECAUSE OF AN UNSPECIFIED NEUROMUSCULAR DISEASE. SHE RECEIVED CARBAMAZEPINE
continued in additional info section...

6. Relevant tests/laboratory data, including dates

ACETOPHENON 38
Carbamazepine (Blood) 33.6
Leukocytes (Polymorphonuclear) 16300
Prothrombin time 84.8
Partial Thromboplastin Time 46
SGOT (AST) 13630
continued in additional info section...

7. Other relevant history, including preexisting medical conditions (e.g. allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

#1 Historical Condition, Neuromuscular disorder NOS

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)

1. CARBAMAZEPINE(CARBAMAZEPINE) (continued)
2. ACETAMINOPHEN(PARACETAMOL) (continued)

2. Dose, frequency & route used	3. Therapy dates (if unknown, give duration)
# 1. 800 mg/day, Oral	# 1. UNK
# 2. 97 mg/kg/day, Oral	# 2. UNK

4. Diagnosis for use (indication)
1. Epilepsy NOS
2. UNK

5. Event abated after use stopped or dose reduced
1. [ ] yes [ ] no [ ] doesn't apply UNK
2. [ ] yes [ ] no [ ] doesn't apply UNK

6. Lot # (if known)
1. UNK
2. UNK

7. Exp. date (if known)
1. UNK
2. UNK

8. Event reappeared after reintroduction
1. [ ] yes [ ] no [ ] doesn't apply UNK
2. [ ] yes [ ] no [ ] doesn't apply UNK

9. NDC # - for product problems only (if known)

10. Concomitant medical products and therapy dates (exclude treatment of event)
NI

G. All Manufacturers

1. Contact office - name/address (& mfring. if devices)
Novartis Pharmaceuticals Corp
Clinical Safety and Epidemiology
Building 419
59 Route 10
East Hanover, NJ 07936 United States

2. Phone number
800 378-8567

3. Report source (check all that apply)
[ ] foreign
[ ] study
[X] literature
[ ] consumer
[X] health professional
[ ] user facility
[ ] company representative
[ ] distributor
[ ] other:

4. Date received by manufacturer
05/08/2001

5. (A)NDA # 16-608
IND #
PLA #
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #

7. Type of report (check all that apply)
[ ] 5-day [X] 15-day
[ ] 10-day [ ] periodic
[ ] initial [X] follow-up # 3

8. Adverse event term(s)
Hepatic failure, Therapeutic agent toxicity

9. Mfr. report number
PHBS1999US10870

E. Initial reporter

1. Name & address
[redacted] United States

phone #

DSS

MAY 2001

2. Health professional?	3. Occupation	4. Initial reporter also sent report to FDA
[X] yes [ ] no	Physician	[ ] yes [ ] no [X] unk

FDA
3500A - Facsimile

SENT TO FDA
MAY 11 2001

09-May-2001 15:10:43

CENTER FOR DRUG EVALUATION AND RESEARCH
RECEIVED
MAY 15 2001
CDR

Medication and Device Experience Report
(continued)

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

Novartis Pharmaceuticals
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service - Food and Drug Administration
Mfr report #
PHBS1999US10870
MFR/Dist report #

FDA Use Only

Individual Safety Report
3723700-5-00-02

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
3. VALPROIC ACID(VALPROIC ACID) Unknown
4

2. Dose, frequency & route used
3 250 mg/day, Oral
4

3. Therapy dates (if unknown, give duration)
3 UNK
4.

4. Diagnosis for use (indication)
3. UNK
4.

5. Event abated after use stopped or dose reduced
3. ☐ yes ☐ no ☐ doesn't apply UNK
4. ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)
3 UNK
4.

7. Exp. date (if known)
3. UNK
4.

8. Event reappeared after reintroduction
3. ☐ yes ☐ no ☐ doesn't apply UNK
4. ☐ yes ☐ no ☐ doesn't apply

9. NDC # - for product problems only (if known)
NA

10. Concomitant medical products and therapy dates (exclude treatment of event)
NA

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35. EVENT DESCRIPTION (cont.)

(800MG/DAY) AND VALPROATE (250MG/DAY) FROM 4 DAYS BEFORE ADMISSION ONWARDS. IN ADDITION, SINGLE DOSES OF ACETOPHENON (600MG) WERE GIVEN BECAUSE SHE HAD SEVERE MENSTRUAL PAIN FROM NEARLY SEVEN DAYS BEFORE ADMISSION ONWARDS. THE MEAN AMOUNT OF ACETOPHENON TAKEN DURING THE PERIOD OF 4 DAYS IMMEDIATELY BEFORE AMISSION WAS CA. 97MG/KG/DAY. A DECLINE IN CONSCIOUSNESS WAS OBSERVED. SHE WAS HOSPITALIZED. THE PERIPHERAL LEUKOCYTE COUNT WAS HIGH (16300/MCL) AND THE BLOOD CARBAMAZEPINE LEVEL WAS INCREASED (33.6MG/L). THE LABORATORY EXAMINATION AFTER ADMISSION SHOWED AST 13630U/L, ALT 9840U/L, TOTAL BILIRUBIN 4.0MG/DL, PT 84.8SECS AND PTT 46SECS. THE BLOOD ACETOPHENON LEVEL WAS 38MG/L. DIAGNOSIS OF CHRONIC POISONING DUE TO ACETOPHENON WAS MADE AND CONSERVATIVE TREATMENT FOR LIVER FAILURE WAS PERFORMED USING N-ACETYLCYSTEINE, BUT SHE DIED 4 DAYS AFTER ADMISSION. ACCORDING TO THE AUTHORS, THE PATIENT DIED FROM LIVER FAILURE DUE TO CHRONIC POISONING OF ACETOPHENON. THEY CONCLUDED THAT ACETOPHENON SHOULD BE ADMINISTERED VERY CAREFULLY IN THE PATIENTS WITH POOR NUTRITIONAL CONDITIONS OR DURING TREATMENT WITH DRUG(S) LIKE CARBAMAZEPINE, SINCE LETHAL EFFECTS MIGHT BE INDUCED BY ITS ADMINISTRATION EVEN AT A LOW DOSE.

FOLLOW-UP INFORMATION WAS RECEIVED ON 21 DEC 1999:
THIS CASE WAS FROM THE USA AND WAS REPORTED IN JAPAN.

Follow-up information was received on 25 Apr 2001:
Case was published in a second article: Journal of Japan Society of Developmental Pharmacology and Therapeutics: vol 13 (1), p 121-122, 2000. (Title: A case of fatal liver due to chronic acetaminophen toxicity.) Full English translation was requested.

Follow-up information was received on 08 May 2001:
Full English translation was received.

Novartis Comment:
ALL LITERATURE REPORTS ARE CONSIDERED "SUSPECTED" FOR REPORTING PURPOSE. THIS IS A SERIOUS LITERATURE REPORT(DEATH) ASSESSED AS UNLISTED ACCORDING TO THE BASIC PRESCRIBING INFORMATION. HOWEVER OTHER ALTERNATIVE CAUSES PROVIDE A POSSIBLE EXPLANATION FOR THE REPORTED ADVERSE EVENT(S): ACETOPHENON POISONING.

B6. RELEVANT TESTS (cont.)

SGPT (ALT) 9840
Bilirubin (total) 4.0

C1. Name (cont.)
Suspect Medication #1: CARBAMAZEPINE(CARBAMAZEPINE) Unknown
Suspect Medication #2: ACETAMINOPHEN(PARACETAMOL) Unknown

G3. Report source literature description

Journal: JAPAN SOCIETY OF PHARMA & THERAPEUTICS
Author:
Title: A CASE OF DEATH FROM LIVER FAILURE ASSOCIATED WITH CHRONIC POISONING DUE TO ACETAMINOPHEN
Volume: 26 Year: 1999 Pages: 5

DSS

A patient who died of hepatic failure due to chronic acetaminophen toxicity

Hidefumi Nakamura[2], Ichiro Yoshida[2], Michael Reed[1], Hirohisa Kato[2]

[1]Rainbow Babies' and Children's Hospital, Cleveland, Ohio

[2]Department of Pediatrics and Child Health, Kurume University

Nihon Shouni Rinshou Yakuri Gakkai Zasshi (The Japanese Journal of Pediatric Developmental Pharmacology and Therapeutics 13(1)121-122/(2000)))

INTRODUCTION

Acetaminophen (APAP) is the drug most frequently used by pediatricians for antipyretic and analgesic purposes. The standard dose is 10 to 15 mg/kg [1]. However, many clinicians choose to use smaller doses. Administration interval is 4 to 6 hours, and maximum daily dose is about 60 mg/kg [1].

APAP is known to induce hepatic damage if given in doses that exceed the therapeutic dosage. It has recently been discovered that, besides acute APAP toxicity, there exists a pathology in the form of chronic toxicity [2]. One of the presenters, Hidefumi Nakamura, encountered a chronic APAP toxicity patient who died after suffering hepatic necrosis. This was a patient whom Nakamura had treated while working at the Rainbow Babies' and Children's Hospital (RBC) in Cleveland, Ohio

(USA). We describe the case below.

CASE STUDY

The patient, a Caucasian female, was 19 years of age and weighed 26.7 kg. She was hospitalized at an institution for neuromuscular diseases and epilepsy, and was receiving respiratory management. 800 mg of carbamazepine (p.o.) q.i.d. was given for an extended period. Beginning four days prior to admission to our hospital, 250 mg of valproic acid (p.o.) b.i.d. and 10 mg of fluoxetine (p.o.), o.d. were given. From around seven days prior to hospital admission, single use of APAP was given for menstrual cramps. In the morning of the day of admission, her consciousness level was seen to drop, and she was transported to a local emergency medical center. Since the level of carbamazepine in her blood was 33.6 mg/L, the physicians determined that the disturbance of consciousness was most likely caused by carbamazepine toxicity. She was thus transferred to RBC's pediatric ICU

After being admitted to RBC, she underwent a battery of biochemical tests. Her AST was 13630 U/L, ALT was 9840 U/L, total bilirubin was 4.0 mg/dL, PT was 84.8 sec., and PTT was 46 sec., showing that she had severe hepatic damage. The pediatric clinical pharmaceutical department was consulted to identify the causes.

We contacted the nurses and other personnel working at the institution to which the patient had been admitted, and obtained the patient's detailed disease history. The following became clear.

Although the patient was extremely thin, an internist had prescribed 600 mg of APAP p.o. per single use (22.5 mg/kg, which was the standard dose in the US for adults).

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For four days immediately prior to being admitted to our hospital, the drug four times a day (90 mg/kg/day) was given. On the basis of this information, chronic APAP toxicity was suspected. The patient's blood was obtained at emergency medical center which had examined her initially, and asked that the concentration of APAP in the blood be measured. It was found that the concentration of APAP in the blood approximately 12 hours after the drug had been last administered was 38 mg/L.

A nomogram devised by Rumack Matthew et al. is commonly used to forecast the severity of acute toxicity (Fig. 1). The graph shows at what APAP blood level hepatic disorders develop after a single administration of massive doses of APAP. It is used as an index for determining whether or not to begin treatment using N-acetylcysteine. After plotting our patient's blood APAP level on this graph, we found that it fell slightly below the "possible risk" line which indicates the risk that hepatic disorders may occur (the point marked with a star in Fig. 1). If this were twelve hours after taking massive doses of APAP singly, and if the patient were a 19-year-old female who was well-nourished and who had not taken carbamazepine and other drugs concomitantly, she would have recovered without suffering any hepatic disorders. However, our patient had been chronically overdosed with APAP (for more than four days), had been taking carbamazepine for extended periods, and was severely undernourished. As a result, she suffered severe hepatic damage. Treatment with N-acetylcysteine proved ineffective, and her hepatic necrosis worsened. The patient died four days after hospitalization.

DISCUSSION

Acute APAP toxicity is said to occur at doses exceeding 125 - 150 mg/kg, and, in

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adults, after a single overdose exceeding 5 - 10 g [2]. Initial symptoms include nausea, vomiting, and generalized malaise. Clinical symptoms seemingly improve temporarily. However, beginning at around 24 to 48 hours after dosing, hepatic damage gradually appears [2]. If treatment using N-acetylcysteine is provided at an early stage (within 8 to 16 hours after administration), severity of hepatic damage may be considerably alleviated [2].

In contrast, it has been recently known that chronic APAP toxicity occurs after multiple overdoses (dosages exceeding the therapeutic range) [2]. According to a summary of 47 chronic APAP toxicity patients by Heubi et al. [3], 47% of the subjects were 2 years old or younger. This is thought to be because the parents had overdosed on APAP syrup by mistake and for other reasons. 88% of the subjects reportedly took APAP for 1 to 5 days, and six of the subjects were given 50 to 75 mg/kg/day: comparable to the therapeutic dosage. Although details of these cases have not been described in the report, we suspect that the patients may have had some risk factors [2] that promoted APAP's hepatic damage-inducing activity, such as malnutrition and concomitant use of drugs that reinforce APAP's hepatic damage-inducing functions (e.g., carbamazepine, phenobarbital, phenytoin, and rifampicin). As was the case with our patient, chronic APAP toxicity often has serious outcomes, since N-acetylcysteine is ineffective in many cases [4]. Unlike acute toxicity, moreover, in chronic toxicity, plasma concentrations are not useful for forecasting the degree of severity. Even in severe patients, depending on the time when the blood was samplinged, their blood APAP levels may have already dropped below the therapeutic range.

A brief explanation follows as to why N-acetylcysteine is effective in acute toxicity cases but not for chronic toxicity, in the light of what is known of the metabolism of

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APAP and its excretion process (see Fig. 2). About 90 to 95% of APAP that has been taken orally and fully absorbed is metabolized by glucuronate conjugation or sulfate conjugation, and then excreted [2]). However, a portion of APAP is metabolized into N-acetyl-p-benzoquinoneimine (NAPQI), a toxic metabolite, by cytochrome P450, a drug metabolic enzyme that exists primarily in the liver. This toxic metabolite is thought to induce hepatic damage by combining irreversibly with hepatic cell proteins and nucleic acids [2]. Glutathione is thought to demonstrate detoxification activity, as its SH group combines with NAPQI [2]. N-acetylcysteine is known to rapidly metabolize into glutathione shortly after administration, and since N-acetylcysteine itself has reduction activity, it combines with NAPQI to demonstrate detoxification effects. As can be seen from this mechanism of action, if hepatic damage has already occurred, then we cannot expect glutathione or N-acetylcysteine to alleviate the severity of hepatic damage.

The following reasons may be cited why our patient's symptoms became severe. To begin with, the patient was severely undernourished and was deficient in glutathione. Excess doses of APAP were repeatedly administered. These were sufficient to make her condition worsen. In addition, she had been given carbamazepine for an extended period of time. This had induced cytochrome P450, which governs APAP's metabolism into NAPQI. As a result, toxicity was further reinforced.

CONCLUSIONS

APAP is administered in smaller doses in Japan than in the US, and is still given primarily through physicians' prescriptions. Instances of APAP toxicity are therefore relatively rare in Japan. Because of this, however, physicians have an extremely low

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awareness of APAP toxicity, and many hospitals do not keep N-acetylcysteine (they orally administer Mucofilin® inhalants) in stock.

At present, APAP is becoming more widely used as an over-the-counter drug. Since it is often used in syrup form, moreover, instances of acetaminophen toxicity may increase in Japan in the future. We, pediatricians, must be fully aware of, and familiarize ourselves with, its presence and treatment methods. APAP is an extremely safe drug as long as it is given in compliance with the correct dosage and administration method. It will continue to play a vital role in the pediatric sector as an effective antipyretic and analgesic drug. However, it can become dangerous when excessive doses are administered. We present our case study at this conference to alert the physicians to this fact.

REFERENCES

1) Taketomo CK, Hodding JH and Kraus DM : Pediatric Dosage Handbook. 6th ed. 1999. Lexi-comp. Ohio.

2) Ellenhorn MJ : Medical Toxicology ; Diagnosis and Treatment of Human Poisoning. 2 nd Ed. New York, Elsevier, 1997,180 - 195.

3) Heubi JE, et al : Therapeutic misadventures with acetaminophen : Hepatotoxicity after multiple doses in children. J Pediatr. 1998 ; 132 : 22-27

4) Kearns GL, et al : Acetaminophen overdose with therapeutic intent. J Pediatr 1998 ; 132 : 5-8. Legends.

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Fig. 1 Plot of Rumack Matthew's nomogram of acute acetaminophen toxicity

Fig. 2 Acetaminophen's metabolic channel and mechanism by which hepatic toxicity occurs